



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA-2001-P-0238, FDA-2010-P-0526, FDA-2010-P-0540, FDA-2011-P-0473]

Determination that the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that OXYCONTIN (oxycodone hydrochloride) extended-release tablets (10 milligrams (mg), 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg) approved under new drug application (NDA) 20-553 were withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for products that reference NDA 20-553.

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SUPPLEMENTARY INFORMATION:

I. Background

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is known generally as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 U.S.C. 355(j)(7)(C); 21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made before approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

OXYCONTIN (oxycodone hydrochloride) extended-release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg (original OxyContin), are the subject of NDA 20-553, held by Purdue Pharma LP (Purdue) and initially approved on December 12, 1995. A reformulated version of these products, OXYCONTIN (oxycodone hydrochloride) extended-release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg (reformulated OxyContin), are the subject of NDA 22-272, also held by Purdue and initially approved on April 5, 2010. Reformulated OxyContin was developed with physicochemical properties that are intended to make the tablet more difficult to manipulate for purposes of abuse or misuse. Both original and reformulated OxyContin are opioid agonist products indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

In correspondence dated August 10, 2010, Purdue notified FDA that it had ceased shipment of original OxyContin, and FDA subsequently moved original OxyContin to the “Discontinued Drug Product List” section of the Orange Book. On April 16, 2013, FDA approved a supplemental application for reformulated OxyContin, approving changes to the product labeling that describe certain abuse-deterrent properties of the reformulated product.

Several parties have submitted citizen petitions under 21 CFR 10.30, requesting that the Agency determine whether original OXYCONTIN (oxycodone hydrochloride) extended-release tablets were voluntarily withdrawn from sale for reasons other than safety or effectiveness.¹

Based on the information available at this time, FDA has determined under § 314.161 that original OxyContin was withdrawn from sale for reasons of safety or effectiveness. FDA

¹ Varam, Inc., Docket No. 2011-P-0473 (June 9, 2011) (10, 15, 20, 30, 40, 50, 80, and 160 mg); Sheppard, Mullin, Richter & Hampton LLP, Docket No. 2010-P-0540 (Oct. 8, 2010) (10, 15, 20, 30, 40, 60, and 80 mg); Lachman Consultant Services, Inc., Docket No. FDA-2010-P-0526) (Sept. 30, 2010) (10, 15, 20, 30, 40, 60, 80, and 160 mg). Lachman also submitted a petition in 2001 concerning just Purdue’s 2001 withdrawal of the 160 mg strength. Docket No. FDA-2001-P-0473 (formerly Docket No.

has reached this determination following a careful review and analysis of the following information: (1) The citizen petitions described previously; (2) the comments submitted to the dockets associated with these petitions; (3) the Agency records and other information concerning original and reformulated OxyContin and the withdrawal of original OxyContin; and (d) data, literature, and other information concerning postmarketing adverse events associated with original OxyContin, reformulated OxyContin, and other extended-release oxycodone products.

II. Initiatives to Address Abuse of Opioid Analgesics

Opioid analgesics are an important component of modern pain management. Abuse and misuse of these products, however, has grown into a public health epidemic. According to the Centers for Disease Control and Prevention, sales of prescription opioids in the United States increased over 300 percent from 1999 to 2008 (Ref. 1). Overdose deaths involving these products increased commensurately over the same period, from 4,000 to 14,800 (Refs. 1 and 2). In 2008 prescription opioids were involved in more overdose deaths than heroin and cocaine combined (Ref. 3). In 2010 the number of overdose deaths in which prescription opioids were involved rose to 16,651, which represented more than 75 percent of all overdose deaths involving prescription drugs (Ref. 4).

FDA, together with other Federal agencies, is working to address this large and growing problem while ensuring that patients in pain have appropriate access to opioid analgesics. FDA has worked to improve the labeling of OxyContin and other opioid analgesics to better warn prescribers and patients of the serious risks associated with abuse and misuse. FDA also has worked extensively with the sponsors of OxyContin and other extended-release or long-acting prescription (ER/LA) opioid analgesics to address these risks through a classwide risk evaluation

and mitigation strategy (REMS)

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf>.

This REMS, approved on July 9, 2012, requires sponsors of ER/LA opioids to make available training for health care professionals on proper prescribing practices and also to distribute educational materials to prescribers and patients on the safe use of these medications.

FDA considers the development of opioid analgesics that can deter abuse and misuse to be a public health priority. Opioid analgesics can be abused orally or by injection, snorting, or smoking and also may be misused in therapeutic contexts. Products may be designed to deter one or more of these methods of abuse or misuse. Following mandates in the 2011 White House prescription drug abuse prevention plan (Ref. 5) and section 1122(c) of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144) (126 Stat. 1075), FDA recently issued a draft guidance to industry on the evaluation and labeling of potentially abuse-deterrent opioid analgesics (Ref. 6).

III. Assessment of Abuse-Deterrent Properties of Reformulated OxyContin

All forms of opioid analgesic abuse are dangerous, and non-oral routes of abuse are particularly dangerous. Intranasal and intravenous opioid abuse is associated with serious adverse events including addiction, overdose, and death (Refs. 7, 8, and 9). Intravenous opioid abuse is associated with HIV and hepatitis B and C infection risk (Ref. 10). Further, as stated in the OxyContin labeling (see section 9.2), injection of OxyContin excipients “can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.” The label is available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272s016lbl.pdf. Intranasal opioid abuse is associated with nasal, palatal, and pharyngeal necrosis (Refs. 7 and 11).

Original OxyContin was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly. Original OxyContin also was manipulated for therapeutic purposes, for example, by crushing the product to sprinkle it onto food or to administer it through a gastric tube. As noted in the boxed warning of the labeling, disruption of the tablet and controlled-release mechanism for abuse or misuse “can lead to rapid release and absorption of a potentially fatal dose of oxycodone.”

FDA has conducted an extensive review of data available to the Agency regarding reformulated OxyContin, including in vitro, pharmacokinetic, clinical abuse potential, and postmarketing study data. The data show that, when compared to original OxyContin, reformulated OxyContin has an increased ability to resist crushing, breaking, and dissolution using a variety of tools and solvents. The data also demonstrate that, when subjected to an aqueous environment, reformulated OxyContin gradually forms a viscous hydrogel. The data also indicate that insufflation of finely crushed reformulated OxyContin was associated with lower “liking” compared to finely crushed original OxyContin in recreational opioid users with a history of intranasal drug abuse. FDA concludes, based on these data and our review of all data and information available to the Agency at this time, that the physicochemical properties of reformulated OxyContin are expected to make abuse via injection difficult and are expected to reduce abuse via the intranasal route. In addition, reformulated OxyContin also may deter certain types of misuse in therapeutic contexts.

Additional postmarketing studies intended to assess the impact of reformulated OxyContin on abuse and misuse in the community also have been conducted; some of these are

still ongoing. FDA has reviewed the available data from these studies and has concluded that they suggest, but do not confirm, a reduction in non-oral abuse. The Agency will continue to review data from these studies as they become available, as well as any other relevant data that may be developed in the future.

FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks. In this case, FDA has considered the abuse potential as part of the Agency's determination of whether the original formulation of OxyContin was withdrawn from sale for reasons of safety or effectiveness. This approach is particularly appropriate here in light of the extensive and well-documented history of OxyContin abuse.

Original OxyContin has the same therapeutic benefits as reformulated OxyContin. Original OxyContin, however, poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks. FDA has determined that OXYCONTIN (oxycodone hydrochloride) extended release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg (approved under new drug application 20-553), were withdrawn from sale for reasons of safety or effectiveness. Accordingly, the Agency will remove OXYCONTIN (oxycodone hydrochloride) extended-release tablets (10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg) approved under NDA 20-553 from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to these drug products.

IV. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), "Policy Impact: Prescription Painkiller Overdoses" (www.cdc.gov/HomeandRecreationalSafety/pdf/PolicyImpact-PrescriptionPainkillerOD.pdf).
2. CDC, "Vital Signs: Overdoses of Prescription Opioid Pain Relievers--United States, 1999-2008," Morbidity and Mortality Weekly Report, vol. 60, No. 43, pp. 1487-1492, 2011 (www.cdc.gov/mmwr/pdf/wk/mm6043.pdf).
3. National Center for Injury Prevention and Control, CDC, "Unintentional Drug Poisoning in the United States" (www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf).
4. Jones, C.M., K.A. Mack, and L.J. Paulozzi, "Pharmaceutical Overdose Deaths, United States, 2010," Journal of the American Medical Association, vol. 309, pp. 657-659, 2013.
5. FDA, "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (<http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf>).

6. FDA, “Draft Guidance for Industry: Abuse-Deterrent Opioids--Evaluation and Labeling,”

(www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf).

7. Katz, N., R.C. Dart, E. Bailey, et al., “Tampering With Prescription Opioids: Nature and Extent of the Problem, Health Consequences, and Solutions,” The American Journal of Drug and Alcohol Abuse, vol. 37, pp. 205-217, 2011.

8. Silva, K., S.M. Schrager, A. Kecojevic, et al., “Factors Associated With History of Non-Fatal Overdose Among Young Nonmedical Users of Prescription Drugs,” Drug and Alcohol Dependence, vol. 128, pp. 104-110, 2013.

9. Degenhardt, L., C. Bucello, B. Mathers, et al., “Mortality Among Regular or Dependent Users of Heroin and Other Opioids: A Systematic Review and Meta-Analysis of Cohort Studies,” Addiction, vol. 106, pp. 32-51, 2011.

10. CDC, “Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance From the CDC and the U.S. Department of Health and Human Services,” Morbidity and Mortality Weekly Report, vol. 61, pp. 1-40, 2012.

11. Alexander, D., K. Alexander, and J. Valentino, “Intranasal Hydrocodone-Acetaminophen Abuse-Induced Necrosis of the Nasal Cavity and Pharynx,” The Laryngoscope, vol. 122, pp. 2378-2381, 2012.

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